What Is the Optimal Follow-up Time to Ascertain the Safety of Proton Pump Inhibitors?

Dear Editors:

We read with great interest the original article by Moayyedi et al[1] about the safety of proton pump inhibitors (PPIs) in patients with coronary or peripheral arterial disease receiving either aspirin or rivaroxaban. We would like to congratulate them, because this is one of the largest prospective placebo-controlled studies, to the best of our knowledge. The authors followed patients for a median time of 3 years and showed that PPIs increased only the risk of enteric infections. However, a question may arise: what is the best follow-up time to ascertain the safety of PPIs? In a recently published meta-analysis regarding the relationship between PPIs and dementia, most of studies reported a follow-up time of 6–9 years.[2] Similarly, studies investigating the bond between PPIs and chronic kidney disease reported a recruitment time of $\leq$14 years[3] and, in this case, an increase of 20%–50% in kidney disease incidence was recorded.

Another observation may be reported for osteopenia. In this study, only patients aging >65 years were recruited; however, it is well-known that the peak of bone mineralization is achieved at the age of 40–45. Therefore, it is presumable that most of patients had already encountered a relevant bone demineralization when they were first randomized to PPI, and we believe that this could be a bias in interpreting the results of fracture outcome.[4] In other words, long-term PPI administration to subjects in the fifth decade of age would have provided more reliable results.

In conclusion, we believe that a period of 3 years may be too short to ascertain a strong link between PPIs administration and some chronic disorders, because the development time of those diseases is too slow. On these bases, a more cautious conclusion about the safety of PPIs should be adopted. Maybe the prolongation of the observation of such patients for >5 years will provide more useful information and, additionally, the number of incident events will increase, so that it could be statistically more relevant, as the authors themselves have correctly pointed out in their Discussion.

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Conflicts of interest
The authors disclose no conflicts.

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Reply. We appreciate the interest shown in our randomized trial, which is by far the largest randomized trial evaluating the safety of PPI therapy.[1] Losurdo et al, and Toshihiro Sugiyama correctly point out that three years may not be enough follow up to determine some of the adverse effects related to long term PPI therapy as acknowledged in our article, but with a median of 3 years of follow up , our study provides the best data available (unbiased because it is randomized and of reasonably high power because of its large size and 3 years of follow-up).[1] Furthermore, the majority of adverse event that has been associated with PPI therapy has at least one database study that notes the association is seen within one year of follow up and in the case of pneumonia the maximal effect is seen within a few days of taking PPI.[2] There are notable exceptions but the vast majority of papers that highlight concerns of PPI therapy show this occurs within one year. Losurdo et al. point out that the peak of bone mineralization is 40-45 yet the mean age of those enrolled was 68 years.[1] However, the mean age of database studies evaluating risk of fracture is often older. Indeed, the first study to show an association of PPI use with fracture had a mean of 77 years at enrolment.[3] Sugiyama points out that physical activity is an important unmeasured variable in assessing bone fracture risk. We agree, and it is a major limitation of observational studies but is not an issue in our large randomized controlled trial as physical activity levels will be expected to be equally distributed across the two randomized arms.

Lazarus et al. and Simin et al. highlight that PPI safety was not the primary outcome of our trial. Simin et al incorrectly state that cancer outcomes (for example) was not a safety outcome in the trial. Although not listed in the design paper, data on cancers were systematically collected every 6 months. Lazarus et al[4] also highlight that the point estimate of the odds ratio for chronic kidney disease was 1.20 and if we exclude those with any borderline renal issues at baseline the 95% confidence intervals will widen. It is interesting that their paper had an initial cohort where patient with a glomerular filtration rate (GFR) of <60 ml/min were excluded but their replication cohort had a cut off of GFR <15ml/min and both gave similar results. We did provide a sensitivity analysis where patients with a GFR <30ml/min were excluded, and this did not change the point estimate or the 95% confidence intervals significantly. The authors estimated the risk of chronic kidney disease to be increased by 76% in their propensity matched analysis[5] and this is significantly higher than the 95% confidence intervals of our estimate (whichever analysis is used). Relatively modest differences in the odds ratios of events with low rates (eg, renal